

**IN THE SPECIFICATION:**

Please amend as follows. Text added to the paragraph is presented in bolded underlined format, while text to be deleted is presented in bolded strike-through format.

Please replace paragraph [0066] with the following paragraph:

[0066] The cDNA for human cytochrome CYP2D6 has been cloned and sequenced (Gonzalez et al., 1988). The genomic sequence of CYP2D6 is also known. CYP2D6 encompasses 9 exons spanning 4.66 kb at chromosomal locus 22q13.1. These and other CYP2D6 sequences are available from databases such as ~~GenBank~~ **GENBANK** (Accession numbers XM\_040063, XM\_040066, XM\_040064, XM\_040062, XM\_040060, XM\_013013, and XM\_040065). The availability of these sequences and the advent of molecular genetics has made possible pharmacogenetic studies of CYP2D6.

Please replace paragraph [0100] with the following paragraph:

[0100] Examples of apparatuses that may be useful for electrophoresis and visualization are an agarose gel electrophoresis apparatus, such as CBS Scientific horizontal mini-gel; a power supply having a constant voltage of 200V or better variable power supply for electrophoresis, such as the BioRad Model 200; photodocumentation apparatus, such as the Alpha Innotech ~~AlphaImager~~ **ALPHAIMAGER** or Polaroid DS34 t; and a transilluminator, e.g., a VWR Model LM-20E or equivalent.

Please replace paragraph [0102] with the following paragraph:

[0102] Centrifugation is carried ~~out~~ in ~~a BioMek~~ **BIOMEK** 2000 or Vortex (VWR; G-560) instruments and centrifuges for spinning PCR trays (~~Sorvall~~ **SORVALL** T6000D). ). The 96-well-plate centrifugation system from ~~Qiagen~~ **QIAGEN** may also be used. Microcentrifuges such as those from Eppendorf are used with Microcentrifuge tubes (from, e.g., National Scientific, CN065S-GT).

Please replace paragraph [0104] with the following paragraph:

[0104] For DNA amplification (PCR), 2 ml MicroTubes with screw caps (Sarstedt; 72.693-005) may be used. A variety of 96-well plates suitable for PCR and other manipulations can be used. In the Examples herein, ABI ~~MicroAmp~~ **MICROAMP** Optical 96-well Reaction Plates (P/N#N801-0560) are used with ABI 96-well Plate Septa (P/N#4315933), or Microseal 96-well PCR microplates (MJ Research, MSP-9601) are used with Microseal A sealing film for microplates (MJ Research, MSA-5001). A 96-place storage system exemplified by VWR #30128-330, is used to store plates containing samples between steps in the assay.

Please replace paragraph [0106] with the following paragraph:

[0106] A PCR cycler capable of processing 96-well plates is used in the Examples. Exemplary PCT thermal cyclers include the ~~GeneAmp~~ **GENEAMP** 9600 (Perkin-Elmer) or the PTC 200 (MJ Research). The MJR PTC 200 has features that are desirable regardless of which instrument is used: heating rates of up to 3°C/second, which reduce reaction times, and rapid temperature homogeneity (e.g.,  $\pm 0.4^{\circ}\text{C}$  within 30 seconds at 90°C). The heating block that is used may be, for example, VWR's Heat Block (VWR, 13259-007).

Please replace paragraph [0108] with the following paragraph:

[0108] In order to process a large number of samples for CYP2D6 genotyping, a multipurpose automated or semi-automated programmable workstation is used (Meldrum, Automation for Genomics, Part One: Preparation for Sequencing, Genome Research, 10:1081-1092, 2000; Meldrum, Automation for Genomics, Part Two: Sequencers, Microarrays, and Future Trends, Genome Research, 10:1288-1303, 2000). Preferred features of the workstation include the ability to rapidly and accurately pipette, dilute and dispense small volumes of liquids. The exemplary ~~programable~~ programmable workstation used herein is the ~~BioMek~~ **BIOMEK** 2000 (Beckman Coulter, Inc.).

Please replace paragraph [0114] with the following paragraph:

[0114] 3.1.1 Agarose, ~~SeaKem~~ **SEAKEM** GTG (FMC 50074). Store ambient (18°C-26°C), stable for 1 year.

Please replace paragraph [0142] with the following paragraph:

[0142] 3.3.2 HotStarTaq™ PCR Core Kit (~~Qiagen~~ **QIAGEN** 203203 or 203205) (HotStarTaq™ enzyme, 25mMg++, M10X buffer & 5X Q Solution), stable for 1 year when stored at -10°C to -30°C.

Please replace paragraph [0150] with the following paragraph:

[0150] 3.5.2 ABI ~~GeneScan~~ **GENESCAN**-120 LIZ Size Standard (P/N4322362), stable for six months when stored at 2 to 10°C.

Please replace paragraph [0158] with the following paragraph:

[0158] 3.8.1.2 Long PCR CYP2D6 and CYP2D6D Duplex Mix is prepared according to the following recipe.

Components	For 114 Rxns
10X <del>Qiagen</del> <b><u>QIAGEN</u></b> PCR Buffer	285.0 µL
5X Q Solution	570.0 µL
25 mM dNTP mix	28.5 µL
5X primer mix (2D6&2D6D) [3.8.1.1, above]	570.0 µL
H2O	1100.1 µL
<b>Total</b>	<b>2553.6 µL</b>

Please replace paragraph [0162] with the following paragraph:

[0162] 3.8.2.2 Long PCR: CYP2D6 and CYP2D6x2 PCR Mix is prepared according to the following recipe.

Components	for 114 Rxns
10X <del>Qiagen</del> <u>QIAGEN</u> PCR Buffer	285.0 $\mu$ L
5X Q Solution	570.0 $\mu$ L
25 mM dNTP mix	28.5 $\mu$ L
5X primer mix (2D6 and 2D6x2) [3.8.2.1, above]	570.0 $\mu$ L
H <sub>2</sub> O	1100.1 $\mu$ L
<b>Total</b>	<b>2553.6 <math>\mu</math>L</b>

Please replace paragraph [0171] with the following paragraph:

[0171] Five (5)  $\mu$ l of ABI SNaPshot Ready Mix, 1  $\mu$ l of Primer Extension Primer Mix and 1  $\mu$ l Sterile H<sub>2</sub>O are combined to a final volume of 7  $\mu$ l per reaction. The Mix is prepared fresh before each use, and kept on ice until used.

Reagent	Per Well	Per Plate*
<del>SnaPshot</del> <u>SNaPshot</u> Ready Mix	5 $\mu$ l	560 $\mu$ l
Extension Primer Mix	1 $\mu$ l	112 $\mu$ l
DH <sub>2</sub> O	1 $\mu$ l	112 $\mu$ l

<b>Total</b>	<b>7 µl</b>	<b>784 µl</b>
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\*Contains extra for aliquot by **BioMek BIOMEK** 2000.

Please replace paragraph [0173] with the following paragraph:

[0173] For each reaction, 1 µl of SAP (1 unit/µl) and 1 µl of water are combined to a final volume of 2 µl. The SAP cocktail is freshly prepared before each use.

<b>Reagent</b>	<b>Per Well</b>	<b>Per Plate*</b>
SAP	1 µl	140 µl
Dh2O	1 µl	140 µl
<b>Total</b>	<b>2 µl</b>	<b>280 µl</b>

\*Contains extra for aliquot by **BioMek BIOMEK** 2000.

Please replace paragraph [0174] with the following paragraph:

[0174] 3.8.8 Loading Mix: Ten (10) µl of Hi-Di Formamide and 0.5 µl **GeneScan GENESCAN** 120 LIZ Size Standard are combined to a final volume of 10.5 µl per sample. Lodging Mix is prepared fresh before each use.

<b>Reagent</b>	<b>Per Well</b>	<b>Per Plate*</b>
Hi-Di Formamide	10 µl	1120 µl
<b>GeneScan <u>GENESCAN</u></b> 120 LIZ Size Standard	0.5 µl	56 µl
<b>Total</b>	<b>10.5 µl</b>	<b>1176 µl</b>

\*This setup is for a full 96 well plate.

Please replace paragraph [0178] with the following paragraph:

[0178] PCR master mix (CYP2D6 and CYP2D6D Duplex Mix) is prepared according to Example 3.8.1.2 and is used in the reaction. The following table describes a recipe that results in a sufficient volume for a full PCR plate (sample tray; 96-wells), and allows for excessive solution to enable pipetting from a trough with an 8-channel pipettor into all PCR wells.

	<b>1 Rxn</b>	<b>Cocktail x 56 (1/2 plate)</b>	<b>Cocktail x 112 (full plate)</b>
Master Mix [3.8.1.2]	22.4 $\mu$ L	1254.4 $\mu$ L	2508.8 $\mu$ L
HotStarTaq	0.3 $\mu$ L	16.8 $\mu$ L	33.6 $\mu$ L
Taq Extender	0.3 $\mu$ L	16.8 $\mu$ L	33.6 $\mu$ L
<b>Qiagen <u>QIAGEN</u> DNA*</b>	2.0 $\mu$ L	----	----
<b>Total</b>	<b>25 <math>\mu</math>L</b>		

Please replace paragraph [0181] with the following paragraph:

[0181] PCR master mix (CYP2D6x2 PCR Mix) is prepared according to Example 3.8.2.2 and is used in the reaction. The following table describes a recipe that results in a sufficient volume for a full PCR plate (sample tray), and allows for excessive solution to enable pipetting from a trough with an 8-channel pipettor into all PCR wells.

	<b>1 Rxn</b>	<b>Cocktail x 56 (1/2 plate)</b>	<b>Cocktail x 112 (full plate)</b>
Master Mix [3.8.2.2]	22.4 $\mu$ L	1254.4 $\mu$ L	2508.8 $\mu$ L units
HotStarTaq	0.3 $\mu$ L	16.8 $\mu$ L	33.6 $\mu$ L
Taq Extender	0.3 $\mu$ L	16.8 $\mu$ L	33.6 $\mu$ L
<b>Qiagen <u>QIAGEN</u> DNA*</b>	2.0 $\mu$ L	----	----
<b>Total</b>	<b>25 <math>\mu</math>L</b>		

Please replace paragraph [0184] with the following paragraph:

[0184] For automated PCR setup on the **BioMek BIOMEK** 2000 robotic workstation, the PCR tray, a box of Robbins 125  $\mu$ L pipet tips, a box of 20  $\mu$ L pipet tips, the **Qiagen QIAGEN** sample tray and the reagent reservoir (trough) are placed at the appropriate positions on the **BioMek BIOMEK** work surface. If the PCR or subsequent steps are set up manually, the same master mix recipe/digestion recipe is used, and the assay proceeds as described below without the **BioMek BIOMEK**, and single or multichannel pipettors and tips are used.

Please replace paragraph [0185] with the following paragraph:

[0185] The master mix is added to the reagent reservoir. Eight positions at the end of the **Qiagen QIAGEN** sample tray are left open for controls. The sample tray is briefly spun down in a plate centrifuge outside of the master mix and template addition area (i.e., in a clean room). The control samples (typically, four positive and two negative controls) are placed in the appropriate positions in the sample tray.

Please replace paragraph [0186] with the following paragraph:

[0186] The **BioMek BIOMEK** station first pipets 23  $\mu$ L of the master mix into each 0.2 ml PCR tray wells, and then adds 2  $\mu$ L specimen DNA or control. The wells are tightly sealed with PCR tube caps or Microseal A film. The sample tray is briefly (~ 5 s) vortexed and spun down for about 30 s in a plate centrifuge at 2,000-6,000g (1,600 rpm in a **Sorvall SORVALL** T6000D centrifuge).

Please replace paragraph [0202] with the following paragraph:

[0202] SAP-digested samples are prepared according to Example 4.5 for loading using a **BioMek BIOMEK** 2000. The SNaPSHOT product is diluted 15-fold with water, and then 2  $\mu$ L of the diluted product is mixed with 10.5  $\mu$ L of the Loading Mix. The plate is covered with septa, vortexed and spun down in the plate centrifuge. The plate is heated at 95°C for 5 minutes, then

immediately placed on ice for 3 minutes or until use. The plate is spun down in a plate centrifuge to collect condensation. The plate is then assembled and loaded onto the ABI3100 Genetic Analyzer.